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Optimal Control Strategies for Syphilis and HIV/AIDS Coinfection Transmission with Cost-Effectiveness Analysis

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ABSTRACT

Syphilis and HIV/AIDS are global health problems with significant impacts on society. The combination of these two infections can worsen the prognosis of patients and increase the economic strain on the health system. This study aims to develop an optimal control model in managing the spread of syphilis and HIV/AIDS coinfection by considering HIV/AIDS treatment, syphilis treatment, and preventive measures through condom use as dynamic control variables. Pontryagin's maximum principle is used to derive the optimality conditions. To theoretically investigate the impact of the control measures, this study analyzed five strategies related to the implementation of these controls using Scilab-2024.0.0 for simulate and evaluate of their effectiveness. The simulation results show that the combination of three control interventions is more effective in decreasing the prevalence of syphilis and HIV/AIDS coinfection compared to the application of one type of control alone. This combination strategy significantly reduces the infection rate by up to 86.04%, emphasizing the importance of a multifaceted intervention approach rather than a single control measure. Furthermore, a cost-effectiveness analysis was conducted by comparing the costs and effectiveness of various control strategies to determine the most efficient and economically feasible option. The results of the comparison indicate that although integrated intervention is the most effective strategy in minimizing infection rates, a strategy that focuses only on preventive measures through the use of condoms is a more efficient option when considering the balance between budget limitations and control effectiveness.

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A. INTRODUCTION

Sexually transmitted infections (STIs), such as syphilis and HIV/AIDS, are still a significant global public health challenge due to their high transmission rates and can cause various complications, including death. In addition to impacting health, STIs contribute to social and economic problems in numerous countries (Kemenkes RI, 2016). Among the various types of STIs, syphilis and HIV remain major concerns worldwide, especially in developing countries (Adawiyah et al., 2021). Globally, the number of new syphilis cases among adults was recorded at 8 million in 2022, while the number of people affected by HIV as of late 2023 reached 39.9 million (WHO, 2023a, 2023b). For conditions in Indonesia, the Ministry of Health revealed an increase in STI cases, especially HIV and syphilis by up to 70 percent in recent years (Kemenkes

RI, 2023). Given the significant health and economic burden posed by these infections, optimizing control strategies and evaluating their cost-effectiveness are crucial for reducing transmission and improving public health outcomes.

Syphilis and HIV can indeed cause health problems for those infected with either of these pathogens. However, the threat becomes more serious when coinfection occurs (Lynn & Lightman in Fan et al., 2021). Several studies have found that sexually transmitted infections, such as syphilis, negatively affect HIV infection because syphilis is linked to an increase in the number of HIV viruses in the blood (viral load) and a decline in CD4 cell counts (Fan et al., 2021; Kotsafti et al., 2016), despite the fact that CD4 cells are types of white blood cells or lymphocytes that hold an essential role in the immune system (Aavani & Allen, 2019). Similarly, HIV can worsen the clinical course of syphilis. HIV-infected syphilis patients are considered at higher risk for neurological complications (brain and nerve disorders) (CDC, 2021), treatment failure, or syphilis reinfection (Lee et al., 2020). In terms of prevention, both infections require comprehensive approach, such as condom use and routine treatment (WHO, 2023a, 2023b).

Syphilis and HIV coinfection has emerged as a public health concern worldwide, with its prevalence varying across different populations and regions. In recent years, the global incidence of this coinfection has increased (Ren et al., 2021). Studies indicate that the prevalence of HIV/AIDS and syphilis coinfection ranges from 8% to 25% (Mata-Marín et al., 2015; Sarigül et al., 2019), depending on the overall burden of both infections in the community and the specific patient batch researched (Fan et al., 2021). In addition, this coinfection is particularly common among men who have sex with men (MSM) in the Asia-Pacific region, where prevalence rates vary from 1.7% to 4.27% (Mahmud et al., 2023).

Based on several studies outlined earlier, syphilis and HIV are a dangerous combination. Hence, strategies are needed that can effectively reduce the prevalence and manage the spread of both infections. Mathematical models play an essential role in describing transmission dynamics and other important factors of infectious diseases that will help policy makers make accurate decisions, design prevention and control intervention strategies, and reduce the rate of disease transmission (Adekola et al., 2020). Previous studies have proposed and developed models of the spread of syphilis and HIV coinfection. Nwankwo and Okuonghae (2018) studied a mathematical model that delineates the spread dynamics of syphilis and HIV coinfection within a population when syphilis treatment is accessible, but HIV treatment is challenging or unavailable. Another study conducted by Wang et al. (2023) formulated an epidemic model for syphilis and HIV coinfection with the assumption that there are only three phases of syphilis progression.

The mathematical model that has been formed by Nwankwo and Okuonghae (2018) is the basis for this research. However, unlike previous research, this study introduces major modifications to improve the applicability and realism of the model. In particular, because syphilis and HIV infections have different clinical developments according to the time of infection, this model assumes that there are two stages of development for each disease. Syphilis infection is classified into early and late stages, while HIV/AIDS is divided into HIV without AIDS symptoms and HIV with AIDS. In addition, a treatment compartment is included to represent individuals with HIV/AIDS undergoing therapy to better reflect actual intervention efforts. These assumptions are adapted from previous research Ayele et al. (2021); Omame et

al. (2021) and designed to address gaps in the literature by balancing model simplicity and important epidemiological factors.

Furthermore, this study examines the analysis of syphilis and HIV/AIDS coinfection models using optimal control theory. This theory utilizes models of mathematics to describe dynamic systems and focuses on determining the best strategies to control or optimize the functioning of these systems (Chazuka et al., 2024). The control model for syphilis and HIV/AIDS coinfection was developed by implementing three control variables consisting of HIV/AIDS treatment, syphilis treatment, and preventive measures such as condom use. The principal aim of optimal control in this modeling is to find the best combination of prevention and treatment measures to minimize the quantity of people who are infected. After that, identify the most cost efficient control strategy. This research is expected to provide insights to make the right decisions in allocating resources and implementing the most effective interventions in controlling the spread of syphilis and HIV/AIDS coinfection.

B. METHODS

This research is an analytical-quantitative study that integrates mathematical modeling, scenario-based simulation, and cost-effectiveness analysis to evaluate optimal strategies for syphilis and HIV/AIDS coinfection control. The data used came from references to relevant previous articles that included epidemiological information, clinical parameters, and the effectiveness of various control efforts.

1. Coinfection Model Formulation

In this part, we present a mathematical model for the spread of syphilis and HIV/AIDS coinfection with control variables. The total population of sexually active humans at time t ($N(t)$) is divided into 12 subpopulations. Each subpopulation represents susceptible individuals (S), monoinfected individuals with early-phase syphilis (I_E), monoinfected individuals with late-phase syphilis (I_L), individuals recovered from syphilis infection (R_S), monoinfected individuals with HIV and asymptomatic for AIDS (I_H), monoinfected individuals with HIV and symptoms for AIDS (I_A), HIV-infected individuals undergoing treatment (T_H), coinfected individuals with early-phase syphilis and HIV without symptoms of AIDS (I_{EH}), coinfected individuals with late-phase syphilis and HIV without symptoms of AIDS (I_{LH}), coinfected individuals with early-phase syphilis and HIV with symptoms of AIDS (I_{EA}), coinfected individuals with late-phase syphilis and HIV with symptoms of AIDS (I_{LA}), and individuals coinfected with HIV and syphilis receiving HIV treatment (T_{SH}). The description and several assumptions used in the formulation of the coinfection model are:

a. At time t, new recruits enter the population with a rate of π through births and the immigration of sexually active individuals.
b. Individuals die in each subpopulation at a constant natural mortality rate μ, with additional disease-induced mortality rates of δ_S for late-phase syphilis and δ_A for HIV with AIDS symptoms.
c. There is no vertical transmission for syphilis and HIV/AIDS infections.
d. Dually infected individuals transmit either syphilis or HIV/AIDS, but not both infections at the same time, as simultaneous transmission is rare (David et al., 2020; Wang et al., 2023).

e. The progression of syphilis infection is divided into two main phases or stages. The primary and secondary phases of syphilis infection are combined into one, which is referred to as syphilis in the early phase. Meanwhile, the tertiary phase of syphilis infection is referred to as late-phase syphilis (Ifeyinwa, 2020; Omame et al., 2021).
f. Susceptible individuals and those singly infected with HIV can become infected with syphilis through effective contact with a person in the early phase of syphilis infection (Nwankwo & Okuonghae, 2018; WHO, 2023b), which is an active infection phase with high transmission potential, with force of infection of

$$\lambda_S = \beta_S \frac{I_E + \theta_1 I_{EH} + \theta_2 I_{EA}}{N},$$

where β_S is the transmission rate of syphilis, the modification parameters θ_1 and θ_2 account for the relative infectiousness from coinfected individuals compared to those with only early-phase syphilis.
g. Similarly, susceptible individuals and those singly infected with syphilis can also acquire HIV when they have effective contact with a person infected with HIV/AIDS (Ayele et al., 2021; CDC, 2022) such that the respective force of infection is equal to

$$\lambda_H = \beta_H \frac{I_H + \eta_1 I_A + \eta_2 I_{EH} + \eta_3 I_{EA} + \eta_4 I_{LH} + \eta_5 I_{LA}}{N},$$

where β_H is the transmission rate of HIV. The modified parameter η_1 describes the relative infectiousness of HIV-infected individuals with AIDS symptoms compared to those suffering from HIV without AIDS symptoms, $\eta_1 \geq 1$ because HIV-infected individuals with AIDS symptoms transmit HIV more easily that individuals who are only infected with HIV without AIDS symptoms (CDC, 2022). Meanwhile, η_2, η_3, η_4, and η_5 account for the relative infectiousness from coinfected individuals.
h. Individuals infected with syphilis are more susceptible to HIV/AIDS infection and conversely (CDC, 2021; David et al., 2020).
i. Individuals infected with early-phase syphilis, whether monoinfected or coinfected, progress to the late phase at progression rates of γ, γ_{S1}, and γ_{S2}.
j. Individuals infected with HIV without AIDS symptoms, whether monoinfected or coinfected, progress to the AIDS stage at progression rates of α, α_{H1}, and α_{H2}.
k. Monoinfected individuals with early-phase syphilis and late-phase syphilis can recover at treatment rates σ_1 and σ_2, respectively, and return to the S compartment at a replase rate of ζ.
l. Individuals infected with asymptomatic HIV and HIV with AIDS symptoms can undergo treatment at rates τ_1 and τ_2, respectively. Similarly, coinfected individuals in subpopulations I_{EH}, I_{LH}, I_{EA}, and I_{LA} receive HIV treatment at rates $\tau_{H1}, \tau_{H2}, \tau_{A1}$, and τ_{A2}, respectively, to enter the T_{SH} subpopulation.

2. Control Variables

An optimal control approach will be conducted to identify the most effective intervention strategies in eradicating the spread of syphilis and HIV/AIDS coinfection over a period of time. The following is an explanation for each control variables that can change over time:

a. $u_1(t)$ represents HIV/AIDS treatment effort through antiretroviral (ARV) therapy, while $u_2(t)$ stands for syphilis treatment effort with antibiotic injection. Both treatments are administered comprehensively with adequate therapy to minimize infections, ensure optimal treatment for individuals diagnosed with syphilis and HIV/AIDS, and prevent further transmission within the population. The implementation of this therapy includes selecting the appropriate type of medication, determining the correct dosage and duration of treatment, conducting periodic medical examinations and monitoring to evaluate the patient's response to therapy.
b. Treatment effors not only focus on administering ARV for HIV and antibiotics for syphilis, but also encompass various aspects that support the success of the therapy.
c. The rate of HIV treatment, which is influenced by treatment efforts u_1 and treatment effectiveness ω_1, is represented by $(1 + u_1\omega_1)\tau$. If there is no effort $(u_1 = 0)$, the treatment rate remains at τ. However, when u_1 is in the range of $0 < u_1 \leq 1$, the constant treatment rate (τ) increases proportionally according to the effectiveness of the implemented intervention. So, $(1 + u_1\omega_1)\tau$ can be interpreted as the rate of individuals who receive and undergo treatment optimally. The greater the value of u_1, the more individuals who get access to effective treatment and achieve undetectable viral load, even though the HIV virus remains in the body.
d. Expression $(1 + u_2\omega_2)\sigma$ represents the rate of syphilis treatment which is influenced by treatment efforts u_2 and treatment effectiveness ω_2. If $u_2 = 0$, the treatment rate remains at σ, while $0 < u_2 \leq 1$, then the constant treatment rate (σ) can increase proportionally depending on the effectiveness of the intervention applied. In other words, $(1 + u_2\omega_2)\sigma$ refers to how quickly or how many individuals infected with syphilis receive treatment and recover in a unit of time. Meanwhile, $u_2\omega_2$ shows the success rate or effectiveness of treatment obtained as a result of efforts to treat syphilis.
e. Futhermore, $u_3(t)$ expresses effort to prevent syphilis and HIV/AIDS infection through the correct and consistent use of male and female condoms to reduce the transmission rate (Momoh et al., 2021; WHO, 2023a). This effort also involves an awareness campaign about the importance of using condom to increase the effectiveness of infection prevention.
f. Ideally, $u_3 = 1$ means that the effort provides full protection againts infection, while $1 - u_3$ indicates the failure of the prevention effort. When $u_3 = 0$, no prevention effort is implemented. These preventive measures are applied to susceptible individuals and those with a monoinfection.

Schematically, the control model of the spread of sphilis and HIV/AIDS coinfection is shown in the compartment diagram as Figure 1. The diagram illustrates the flow of individuals between compartments or subpopulations.

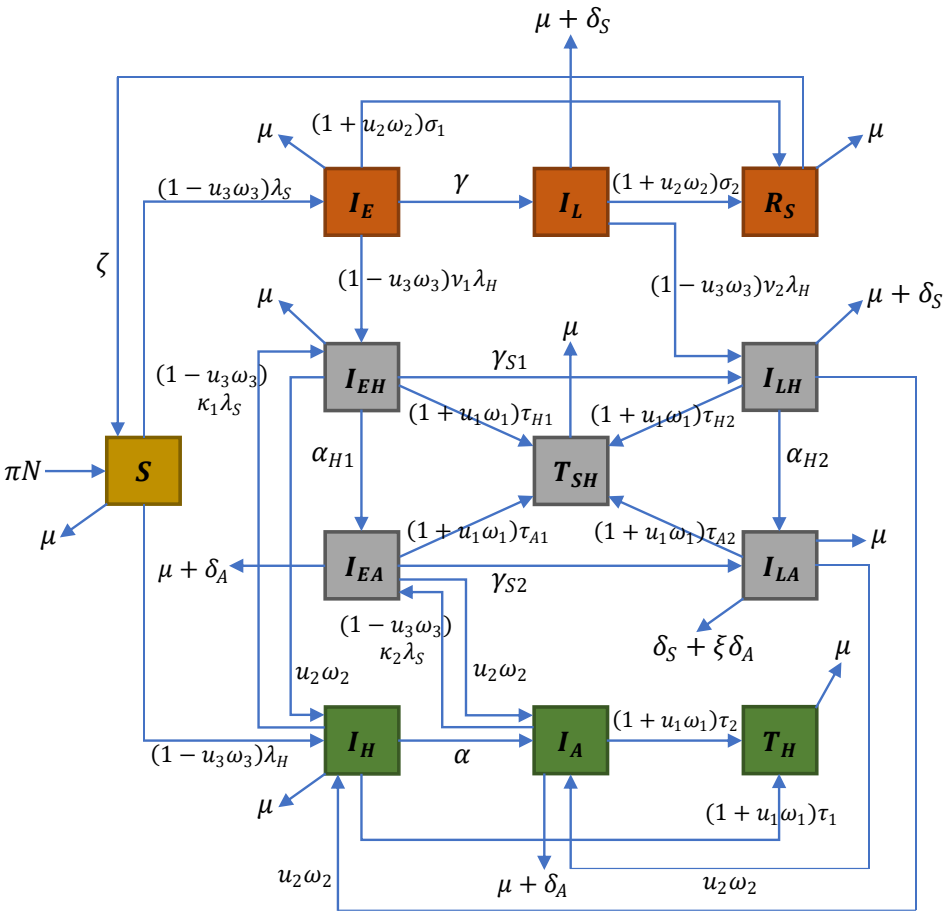


Figure 1. Syphilis and HIV/AIDS Coinfection Compartment Diagram with Control Variables

The proportion of each compartment in the coinfection model can be established by defining the following variables:

$$s = \frac{S}{N}, i_e = \frac{I_E}{N}, i_l = \frac{I_L}{N}, r_s = \frac{R_S}{N}, i_h = \frac{I_H}{N}, i_a = \frac{I_A}{N}, p_h = \frac{T_H}{N}, i_{eh} = \frac{I_{EH}}{N}, \\ i_{lh} = \frac{I_{LH}}{N}, i_{ea} = \frac{I_{EA}}{N}, i_{la} = \frac{I_{LA}}{N}, p_{sh} = \frac{T_{SH}}{N}. \tag{1}$$

Based on the compartment diagram in Figure 1 and new variables (1), the control model is formulated as system of nonlinear differential equations (2), known as state system. This system describes the rate of change in each subpopulation (or state variable) over time.

$$\begin{aligned}
\frac{ds}{dt} &= \pi + \zeta r_s - (1 - u_3\omega_3)\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})s \\
&\quad - (1 - u_3\omega_3)\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})s - \mu s, \\
\frac{di_e}{dt} &= (1 - u_3\omega_3)\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})s \\
&\quad - (1 - u_3\omega_3)\nu_1\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})i_e \\
&\quad - \big((1 + u_2\omega_2)\sigma_1 + \gamma + \mu\big)i_e,
\end{aligned} \tag{2}$$

$$\frac{di_l}{dt} = \gamma i_e - (1-u_3\omega_3)\nu_2\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})i_l - \big((1+u_2\omega_2)\sigma_2 + \mu + \delta_S\big)i_l,$$

$$\frac{dr_s}{dt} = (1+u_2\omega_2)\sigma_1 i_e + (1+u_2\omega_2)\sigma_2 i_l - (\zeta+\mu)r_s,$$

$$\frac{di_h}{dt} = (1-u_3\omega_3)\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})s + u_2\omega_2 i_{eh} + u_2\omega_2 i_{lh} - (1-u_3\omega_3)\kappa_1\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})i_h - (\alpha + (1+u_1\omega_1)\tau_1 + \mu)i_h,$$

$$\frac{di_a}{dt} = u_2\omega_2 i_{ea} + u_2\omega_2 i_{la} + \alpha i_h - (1-u_3\omega_3)\kappa_2\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})i_a - \big((1+u_1\omega_1)\tau_2 + \mu + \delta_A\big)i_a,$$

$$\frac{dp_h}{dt} = (1+u_1\omega_1)\tau_1 i_h + (1+u_1\omega_1)\tau_2 i_a - \mu p_h,$$

$$\frac{di_{eh}}{dt} = (1-u_3\omega_3)\nu_1\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})i_e + (1-u_3\omega_3)\kappa_1\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})i_h - (u_2\omega_2 + \gamma_{S1} + \alpha_{H1} + (1+u_1\omega_1)\tau_{H1} + \mu)i_{eh},$$

$$\frac{di_{lh}}{dt} = (1-u_3\omega_3)\nu_2\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la})i_l + \gamma_{S1} i_{eh} - (u_2\omega_2 + \alpha_{H2} + (1+u_1\omega_1)\tau_{H2} + \mu + \delta_S)i_{lh},$$

$$\frac{di_{ea}}{dt} = (1-u_3\omega_3)\kappa_2\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})i_a + \alpha_{H1} i_{eh} - (u_2\omega_2 + \gamma_{S2} + (1+u_1\omega_1)\tau_{A1} + \mu + \delta_A)i_{ea},$$

$$\frac{di_{la}}{dt} = \gamma_{S2} i_{ea} + \alpha_{H2} i_{lh} - (u_2\omega_2 + (1+u_1\omega_1)\tau_{A2} + \mu + \delta_S + \xi\delta_A)i_{la},$$

$$\frac{dp_{sh}}{dt} = (1+u_1\omega_1)\tau_{H1} i_{eh} + (1+u_1\omega_1)\tau_{H2} i_{lh} + (1+u_1\omega_1)\tau_{A1} i_{ea} + (1+u_1\omega_1)\tau_{A2} i_{la} - \mu p_{sh}.$$

Before starting the epidemiological model simulation (1), determining the initial values for each subpopulation is crucial to ensuring the accurate implementation and analysis of the system. These initial values provide an overview of the system's starting conditions at $t = 0$ for solving the system of differential equations. Below are the initial values assigned to each subpopulation:

$$0 \le s(0) = s_0, i_e(0) = i_{e_0}, i_l(0) = i_{l_0}, r_s(0) = r_{s_0}, i_h(0) = i_{h_0}, \; i_a(0) = i_{a_0}, \; p_h(0) = p_{h_0}, i_{eh}(0) = i_{eh_0}, i_{lh}(0) = i_{lh_0}, i_{ea}(0) = i_{ea_0}, i_{la}(0) = i_{la_0}, p_{sh}(0) = p_{sh_0} \le 1 \text{ and } N(0) = 1. \tag{3}$$

We also assume that, at the end of period t_f, the proportion of individuals in each subpopulation is not specified, namely

$$s(t_f), i_e(t_f), i_l(t_f), r_s(t_f), i_h(t_f), i_a(t_f), p_h(t_f), i_{eh}(t_f), i_{lh}(t_f), i_{ea}(t_f), i_{la}(t_f), p_{sh}(t_f) \text{ are free.} \tag{4}$$

All parameters are positive and the explanation of the notation in the system of equations (2) is explained as Table 1 below.

Table 1. Interpretation and Parameter Values for the Coinfection Model

Parameter	Interpretation	Value (year^{-1})	Reference
Π	Recruitment rate	$\pi = \mu$	-
μ	Natural death rate	0.02	Emvudu et al. (2016)
β_S	Syphilis transmission rate	6.1	Nwankwo and Okuonghae (2018)
β_H	HIV/AIDS transmission rate	0.99	Nwankwo and Okuonghae (2018)
σ_1, σ_2	Treatment rates of singly infected individuals, respectively for early-phase and late-phase syphilis	1, 0.04	Nwankwo and Okuonghae (2018)
γ	Progression rate of singly infected individuals from early-phase syphilis to late-phase syphilis	0.2	Omame et al. (2021)
γ_{S1}, γ_{S2}	Progression rates of syphilis infection in dually infected individuals from I_{EH} to I_{LH} and I_{EA} to I_{LA}	0.3, 0.4	Nwankwo and Okuonghae (2018)
α	Progression rate of singly infected individuals from HIV (I_H) to AIDS phase (I_A)	0.07	Ayele et al. (2021)
α_{H1}, α_{H2}	Rates of progression of HIV infection in dually infected individuals from I_{EH} to I_{EA} and I_{LH} to I_{LA}	0.08, 0.09	Assumed
κ_1, κ_2	Modification parameters that account for the susceptibility of individuals with HIV/AIDS to syphilis infection; $\kappa_1, \kappa_2 > 1$	1.3	Nwankwo and Okuonghae (2018)
ν_1, ν_2	Modification parameters that account for the susceptibility of individuals with syphilis to HIV/AIDS infection; $\nu_1, \nu_2 > 1$	2.8	Nwankwo and Okuonghae (2018)
η_1	Modification parameters that account for relative transmission in subpopulation I_A	1.2	Emvudu et al. (2016)
$\eta_2, \eta_3, \eta_4, \eta_5$	Modification parameters that account for relative transmission in the respective subpopulations I_{EH}, I_{EA}, I_{LH}, and I_{LA}	1.3, 1.4, 1.48, 1.6	Nwankwo and Okuonghae (2018)
θ_1, θ_2	Modification parameters that account for relative transmission in dually infected individuals, respectively for subpopulations I_{EH} and I_{EA}	1.5, 1.7	Nwankwo and Okuonghae (2018)
δ_S	Death rate from late-phase syphilis	0.06849	Omame et al. (2021)
δ_A	Death rate due to AIDS	0.094	Emvudu et al. (2016)
τ_1, τ_2	Treatment rates of singly infected individuals, respectively for HIV (I_H) and AIDS phase (I_A)	0.25	Ayele et al. (2021)

Parameter	Interpretation	Value (year^{-1})	Reference
τ_{H1}, τ_{H2}, τ_{A1}, τ_{A2}	HIV/AIDS only treatment rates related to coinfection in the respective subpopulations I_{EH}, I_{LH}, I_{EA}, and I_{LA}	0.25	Assumed
ξ	Modification parameters relating to the relative mortality of AIDS affected individuals, $\xi \geq 1$ indicates that late-phase syphilis infection in subpopulation I_{LA} increases the risk of death compared to individuals with AIDS (I_A) (Getaneh et al., 2023).	1.1	Assumed
ζ	Syphilis relapse rate	0.0015	Jing et al. (2021)
ω_1	Effectiveness of HIV/AIDS treatment	0.8	Ayalew et al. (2016)
ω_2	Effectiveness of syphilis treatment	0.9	Clement et al. (2019)
ω_3	Effectiveness of condom usage	0.93	Chazuka et al. (2024)

C. RESULT AND DISCUSSION

1. Sensitivity Analysis

In this section, a sensitivity analysis of the parameters to the basic reproduction number ($\mathcal{R}_0$) will be carried out. The basic reproduction number relates to the ability of a disease to spread in a population. An $\mathcal{R}_0 > 1$ value indicates that the infection can spread in the population, while an $\mathcal{R}_0 < 1$ indicates that the infection will decrease and eventually disappear. This sensitivity analysis aims to determine the extent to which each parameter influences $\mathcal{R}_0$ in the mathematical model (2). In general, sensitivity analysis is conducted by by considering the sensitivity index value with the following formula:

$$\Upsilon_p^{\mathcal{R}_{0S}} = \frac{\partial \mathcal{R}_{0S}}{\partial p} \times \frac{p}{\mathcal{R}_{0S}}, \qquad \Upsilon_p^{\mathcal{R}_{0H}} = \frac{\partial \mathcal{R}_{0H}}{\partial p} \times \frac{p}{\mathcal{R}_{0H}},$$

where p denotes each parameter to be measured for its sensitivity index (ELmojtaba et al., 2024). The basic reproduction number of the system with control (2) is given as follows:

$$\begin{aligned}\mathcal{R}_0 &= max\left\{\mathcal{R}_{0S}, \mathcal{R}_{0H}\right\} \\ &= max\left\{\frac{\beta_S(1-u_3\omega_3)}{\gamma+\mu+\sigma_1(1+u_2\omega_2)}, \frac{\beta_H\left(\delta_A+\alpha\eta_1+\mu+\tau_2(1+u_1\omega_1)\right)(1-u_3\omega_3)}{\left(\alpha+\mu+\tau_1(1+u_1\omega_1)\right)\left(\delta_A+\mu+\tau_2(1+u_1\omega_1)\right)}\right\}.\end{aligned}$$

Furthermore, the sensitivity index is obtained as presented in Tables 2 and 3. Each parameter uses the values in Table 1, where the control u_1, u_2, and u_3 are assumed to be constant and seen as model parameters (Nainggolan et al., 2025). The values $u_i = 0, i = 1,2,3$ indicate no intervention, while $u_i = 0.2, 0.5, 0.8, \text{and } 1.0$ indicate control proportions of 20%, 50%, 80%, and 100%, respectively. Based on the sensitivity index, parameters with a positive index significantly increase the burden of disease if the value increases. Conversely, parameters with a negative sensitivity index reduce the burden of disease as the value of the parameter increases, while

other factors remain constant. In other words, as the value increases, $\mathcal{R}_0$ decreases, thus reducing the endemicity of the disease in the population.

Table 2. Sensitivity Indices of $\mathcal{R}_{0_S}$

Parameter	$u_2, u_3 = 0$	$u_2, u_3 = 0.2$	$u_2, u_3 = 0.5$	$u_2, u_3 = 0.8$	$u_2, u_3 = 1.0$
β_S	1	1	1	1	1
ω_3	0	−0.228501	−0.869159	−2.90625	−13.2857
γ	−0.163934	−0.142875	−0.11976	−0.103093	−0.0943396
μ	−0.0163934	−0.0142875	−0.011976	−0.0103093	−0.00943396
σ_1	−0.819672	−0.842857	−0.868263	−0.886598	−0.896226
ω_2	0	−0.128571	−0.269461	−0.371134	−0.424528

Table 2 presents the results of parameter sensitivity analysis to $\mathcal{R}_{0_S}$ in various control scenarios determined by the values of u_2 and u_3. The results of the analysis show that the syphilis transmission rate (β_S) has the greatest influence on $\mathcal{R}_{0_S}$ with a sensitivity value of 1 in all conditions, indicating that an increase in β_S directly increases $\mathcal{R}_{0_S}$ and accelerates the spread of infection. The parameter σ_1 (rate of syphilis treatment) also shows a significant impact on $\mathcal{R}_{0_S}$ with a negative sensitivity value, which means that an increase in σ_1 can help reduce the rate of disease spread. In addition, the parameter ω_3 (effectiveness of condom use) shows an increasing effect as the value of u_3 increases. This indicates that this intervention is very effective in suppressing $\mathcal{R}_{0_S}$. Overall, these results confirm that the most effective control strategy for suppressing the spread of disease is to reduce the rate of transmission, increase the rate of treatment, and increase the effectiveness of intervention u_3, as shown in Table 3.

Table 3. Sensitivity Indices of $\mathcal{R}_{0_H}$

Parameter	$u_1, u_3 = 0$	$u_1, u_3 = 0.2$	$u_1, u_3 = 0.5$	$u_1, u_3 = 0.8$	$u_1, u_3 = 1.0$
β_H	1	1	1	1	1
δ_A	−0.0484203	−0.0400503	−0.0310534	−0.024784	−0.0216049
α	−0.0183824	−0.0120794	−0.00580624	−0.00184211	-2.63538×10^{-17}
η_1	0.1875	0.172131	0.153285	0.138158	0.12963
τ_2	−0.128777	−0.123559	−0.115624	−0.108101	−0.103428
ω_1	0	−0.122306	−0.260308	−0.362186	−0.416338
τ_1	−0.735294	−0.763158	−0.795455	−0.82	−0.833333
μ	−0.0691257	−0.0611529	−0.0520616	−0.0452732	−0.0416338
ω_3	0	−0.228501	−0.869159	−2.90625	−13.2857

Table 3 presents the sensitivity index of various $\mathcal{R}_{0_H}$ parameters in various control scenarios determined by the values of u_1 and u_3. The results of the analysis show that the rate of HIV transmission (β_H) has the greatest influence on $\mathcal{R}_{0_H}$ with a sensitivity index of 1 in all conditions, which means that an increase in β_H will directly increase $\mathcal{R}_{0_H}$ and accelerate the spread of infection. In addition, τ_1 (HIV treatment rate) has a fairly large negative sensitivity value, ranging from -0.735294 to -0.833333. This shows that an increase in the treatment rate in infected individuals can reduce $\mathcal{R}_{0_H}$, so that strategies to increase access to treatment are an important factor in disease control. The ω_3 parameter (effectiveness of condom use) also

shows a significant effect, where the sensitivity index increases negatively with an increase in u_3. At $u_3 = 1$, the sensitivity index reaches -13.2857, indicating that this intervention is very effective in suppressing $\mathcal{R}_{0_H}$ and controlling the spread of infection. Overall, these results indicate that the most effective control strategy for suppressing the spread of the disease is to reduce the rate of HIV transmission, increase the rate of treatment**,** and increase the effectiveness of u_3 interventions. Policy implementation, such as increasing treatment coverage, reducing contact, and stricter intervention strategies can significantly help lower the $\mathcal{R}_{0_H}$ value and control infections in the population.

2. Analysis of Optimal Control and System of Optimality

The goal of optimization is to minimize the proportion of infected individuals, both singly infected and coinfected. However, when considering control measures, the cost associated with implementing each control measure is kept to a minimum over a certain period. The application of control variables increases the costs, while decreasing the proportion of infected individuals. Therefore, the cost function is represented as a quadratic form $E_i u_i^2$, so the objective functional for the model with controls in system (2) can be expressed:

$$\begin{aligned} &\mathcal{J}(u_1, u_2, u_3) \\ &\quad = \int_0^{t_f} \Big[D_1 i_e + D_2 i_l + D_3 i_h + D_4 i_a + D_5 i_{eh} + D_6 i_{lh} + D_7 i_{ea} + D_8 i_{la} \\ &\quad + \frac{1}{2}(E_1 u_1^2 + E_2 u_2^2 + E_3 u_3^2) \Big] dt, \end{aligned} \tag{5}$$

where D_j $(j = 1, 2, 3, 4, 5, 6, 7, 8)$ is the non-negative coefficient for each state variable $i_e, i_l, i_h, i_a, i_{eh}, i_{lh}, i_{ea}, i_{la}$ and E_1, E_2, E_3 is the relative cost of prevention and treatment associated with controls u_1, u_2, u_3, while t_f represents the final time. In other words, the optimal control problem is concerned with finding the optimal control variables $\mathcal{u}^* = (u_1^*, u_2^*, u_3^*)$ such that

$$\mathcal{J}(u_1^*, u_2^*, u_3^*) = \min_{u_1, u_2, u_3 \in \Omega} \mathcal{J}(u_1, u_2, u_3).$$

All efforts (controls) made are limited, with the proportion of treatment and condom use controls can each be applied to a maximum of 100% or each individual is applied a control. The controls $u_1(t), u_2(t), u_3(t)$ are Lebesgue integrable functions, ensuring that the interventions are measurable and can be effectively applied over time, as defined by

$$\Omega = \{(u_1, u_2, u_3) \colon 0 \le u_i(t) \le 1, \text{for } i = 1, 2, 3, \text{and } t \in [0, t_f]\}, \tag{6}$$

with Ω representing the set of admissible control variables. Further, the optimal control problem is solved by satisfying the conditions of Pontryagin's maximum principle. However, the condition of optimality can be formulated by first defining a Hamiltonian function $\mathcal{H}(x, t, \mathcal{u}, q)$, which integrates the state system, control variables, and costate variables (Athans

& Falb, 2007; Tu, 1984). In general, $\mathcal{H}(x,t,u,q)$ is defined based on model (2) and the objective functional (5), resulting in the following equation:

$$\mathcal{H}(x,t,u,q) = D_1 i_e + D_2 i_l + D_3 i_h + D_4 i_a + D_5 i_{eh} + D_6 i_{lh} + D_7 i_{ea} + D_8 i_{la} + \frac{1}{2}\sum_{i=1}^{3} E_i u_i^2 + \sum_{r=1}^{12} q_r(t) c_r,$$

where $q_r(t) \neq 0$ for $r = 1, 2, 3, \dots, 12$ are the costate variables, it serves as an additional variable that captures the sensitivity of the objective function to changes in the state variable within a dynamic system and c_r is the right-hand portion of the system of equations (1). According Pontryagin's maximum principle, if the control $u^* = (u_1^*, u_2^*, u_3^*)$ and the corresponding state $x^* = (s^*, i_e^*, i_l^*, r_s^*, i_h^*, i_a^*, p_h^*, i_{eh}^*, i_{lh}^*, i_{ea}^*, i_{la}^*, p_{sh}^*)$ are an optimal pair of the optimal control problem (2)-(5), the following conditions must be satisfed.

$$\frac{\partial x}{\partial t} = \frac{\partial \mathcal{H}}{\partial q_r}, \tag{7}$$

$$\frac{\partial \mathcal{H}}{\partial u} = 0, \tag{8}$$

$$\frac{\partial q_r}{\partial t} = -\frac{\partial \mathcal{H}}{\partial x}. \tag{9}$$

Condition (7) gives the state system (2) with initial conditions (3), while optimal control is achieved by satisfying condition (8) and the costate system is determined by completing term (9) in the following Theorem 1.

Theorem 1. *Let* $x^* := (s^*, i_e^*, i_l^*, r_s^*, i_h^*, i_a^*, p_h^*, i_{eh}^*, i_{lh}^*, i_{ea}^*, i_{la}^*, p_{sh}^*)$ *be the optimal state solution associated with the optimal control* $u^* = (u_1^*, u_2^*, u_3^*)$ *for the optimal control problem* $(2) - (5)$, *by the given initial conditions* $s(0)$, $i_e(0)$, $i_l(0)$, $r_s(0)$, $i_h(0)$, $i_a(0)$, $p_h(0)$, $i_{eh}(0)$, $i_{lh}(0)$, $i_{ea}(0)$, $i_{la}(0)$, $p_{sh}(0)$ *and fixed final time* t_f. *Consequently, there exist costate variables* $q_r, r = 1, 2, 3, \dots, 12$ *satisfying the following equations*:

$$\begin{aligned}
\frac{dq_1}{dt} &= (q_1 - q_2)(1 - u_3\omega_3)\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea}) \\
&\quad + (q_1 - q_5)(1 - u_3\omega_3)\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la}) + q_1\mu, \\
\frac{dq_2}{dt} &= -D_1 + \big((q_1 - q_2)s + (q_5 - q_8)\kappa_1 i_h + (q_6 - q_{10})\kappa_2 i_a\big)(1 - u_3\omega_3)\beta_S \\
&\quad + (q_2 - q_8)(1 - u_3\omega_3)\nu_1\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la}) \\
&\quad + (q_2 - q_4)(1 + u_2\omega_2)\sigma_1 + (q_2 - q_3)\gamma + q_2\mu, \\
\frac{dq_3}{dt} &= -D_2 + (q_3 - q_9)(1 - u_3\omega_3)\nu_2\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la}) \\
&\quad + (q_3 - q_4)(1 + u_2\omega_2)\sigma_2 + q_3(\mu + \delta_S), \\
\frac{dq_4}{dt} &= (q_4 - q_1)\zeta + q_4\mu,
\end{aligned} \tag{10}$$

$$\frac{dq_5}{dt} = -D_3 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H + (q_5 - q_8)(1 - u_3\omega_3)\kappa_1\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea}) + (q_5 - q_6)\alpha + (q_5 - q_7)(1 + u_1\omega_1)\tau_1 + q_5\mu,$$

$$\frac{dq_6}{dt} = -D_4 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H\eta_1 + (q_6 - q_{10})(1 - u_3\omega_3)\kappa_2\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea}) + (q_6 - q_7)(1 + u_1\omega_1)\tau_2 + q_6(\mu + \delta_A),$$

$$\frac{dq_7}{dt} = q_7\mu,$$

$$\frac{dq_8}{dt} = -D_5 + \big((q_1 - q_2)s + (q_5 - q_8)\kappa_1 i_h + (q_6 - q_{10})\kappa_2 i_a\big)(1 - u_3\omega_3)\beta_S\theta_1 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H\eta_2 + (q_8 - q_5)u_2\omega_2 + (q_8 - q_9)\gamma_{S1} + (q_8 - q_{10})\alpha_{H1} + (q_8 - q_{12})(1 + u_1\omega_1)\tau_{H1} + q_8\mu,$$

$$\frac{dq_9}{dt} = -D_6 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H\eta_4 + (q_9 - q_5)u_2\omega_2 + (q_9 - q_{11})\alpha_{H2} + (q_9 - q_{12})(1 + u_1\omega_1)\tau_{H2} + q_9(\mu + \delta_S),$$

$$\frac{dq_{10}}{dt} = -D_7 + \big((q_1 - q_2)s + (q_5 - q_8)\kappa_1 i_h + (q_6 - q_{10})\kappa_2 i_a\big)(1 - u_3\omega_3)\beta_S\theta_2 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H\eta_3 + (q_{10} - q_6)u_2\omega_2 + (q_{10} - q_{11})\gamma_{S2} + (q_{10} - q_{12})(1 + u_1\omega_1)\tau_{A1} + q_{10}(\mu + \delta_A),$$

$$\frac{dq_{11}}{dt} = -D_8 + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)(1 - u_3\omega_3)\beta_H\eta_5 + (q_{11} - q_6)u_2\omega_2 + (q_{11} - q_{12})(1 + u_1\omega_1)\tau_{A2} + q_{11}(\mu + \delta_S + \xi\delta_A),$$

$$\frac{dq_{12}}{dt} = q_{12}\mu,$$

with the transversality condition $q_r(t_f)$ *for* $r = 1, 2, 3, \dots, 12.$ (11)

Additionally, when boundary conditions $0 \le u_i \le 1, i = 1, 2, 3$ are utilized in the control, the control set can be characterized by

$$\begin{aligned} u_1^*(t) &= min\left\{max\left\{0, \frac{z_1}{E_1}\right\}, 1\right\}, \\ u_2^*(t) &= min\left\{max\left\{0, \frac{z_2}{E_2}\right\}, 1\right\}, \\ u_3^*(t) &= min\left\{max\left\{0, \frac{z_3}{E_3}\right\}, 1\right\}. \end{aligned} \tag{12}$$

where

$$z_1 = (q_5 - q_7)\omega_1\tau_1 i_h + (q_6 - q_7)\omega_1\tau_2 i_a + (q_8 - q_{12})\omega_1\tau_{H1} i_{eh} + (q_9 - q_{12})\omega_1\tau_{H2} i_{lh} + (q_{10} - q_{12})\omega_1\tau_{A1} i_{ea} + (q_{11} - q_{12})\omega_1\tau_{A2} i_{la},$$

$$z_2 = (q_2 - q_4)\omega_2\sigma_1 i_e + (q_3 - q_4)\omega_2\sigma_2 i_l + (q_8 - q_5)\omega_2 i_{eh} + (q_9 - q_5)\omega_2 i_{lh} + (q_{10} - q_6)\omega_2 i_{ea} + (q_{11} - q_6)\omega_2 i_{la},$$

$$z_3 = \big((q_2 - q_1)s + (q_8 - q_5)\kappa_1 i_h + (q_{10} - q_6)\kappa_2 i_a\big)\omega_3\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea}) + \big((q_5 - q_1)s + (q_8 - q_2)\nu_1 i_e + (q_9 - q_3)\nu_2 i_l\big)\omega_3\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh} + \eta_5 i_{la}).$$

Proof.

Let the optimal control u^* and x^* be the corresponding solutions to the optimality problem of model (2). To prove Theorem 1, the derivative operation is applied to the Hamiltonian function $\mathcal{H}(x,t,u,q)$ with respect to each state variable by employing Pontryagin's maximum principle. The costate system can be determined by solving condition (9), as shown below:

$$\begin{aligned}
&\frac{\partial q_1}{\partial t} = -\frac{\partial \mathcal{H}}{\partial s}, && \frac{\partial q_4}{\partial t} = -\frac{\partial \mathcal{H}}{\partial r_s}, && \frac{\partial q_7}{\partial t} = -\frac{\partial \mathcal{H}}{\partial p_h}, && \frac{\partial q_{10}}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_{ea}},\\
&\frac{\partial q_2}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_e}, && \frac{\partial q_5}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_h}, && \frac{\partial q_8}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_{eh}}, && \frac{\partial q_{11}}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_{la}},\\
&\frac{\partial q_3}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_l}, && \frac{\partial q_6}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_a}, && \frac{\partial q_9}{\partial t} = -\frac{\partial \mathcal{H}}{\partial i_{lh}}, && \frac{\partial q_{12}}{\partial t} = -\frac{\partial \mathcal{H}}{\partial p_{sh}}.
\end{aligned} \tag{13}$$

Thus, the final conditions (4) are free then the transversality condition (11) must be satisfied at the final time t_f. Furthermore, by differentiating the Hamiltonian function $\mathcal{H}(x,t,u,q)$ with respect to each control variable u_1, u_2, and u_3, the following equation is used to determine the optimal control function.

$$\begin{aligned}
\frac{\partial \mathcal{H}}{\partial u_1} &= E_1 u_1 + (q_7 - q_5)\omega_1\tau_1 i_h + (q_7 - q_6)\omega_1\tau_2 i_a + (q_{12} - q_8)\omega_1\tau_{H1} i_{eh}\\
&\quad + (q_{12} - q_9)\omega_1\tau_{H2} i_{lh} + (q_{12} - q_{10})\omega_1\tau_{A1} i_{ea} + (q_{12} - q_{11})\omega_1\tau_{A2} i_{la} = 0,\\
\frac{\partial \mathcal{H}}{\partial u_2} &= E_2 u_2 + (q_4 - q_2)\omega_2\sigma_1 i_e + (q_4 - q_3)\omega_2\sigma_2 i_l + (q_5 - q_8)\omega_2 i_{eh} + (q_5 - q_9)\omega_2 i_{lh}\\
&\quad + (q_6 - q_{10})\omega_2 i_{ea} + (q_6 - q_{11})\omega_2 i_{la} = 0,\\
\frac{\partial \mathcal{H}}{\partial u_3} &= E_3 u_3 + \big((q_1 - q_2)s + (q_5 - q_8)\kappa_1 i_h + (q_6 - q_{10})\kappa_2 i_a\big)\omega_3\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})\\
&\quad + \big((q_1 - q_5)s + (q_2 - q_8)\nu_1 i_e + (q_3 - q_9)\nu_2 i_l\big)\omega_3\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea}\\
&\quad + \eta_4 i_{lh} + \eta_5 i_{la}) = 0,
\end{aligned} \tag{14}$$

at $u_1 = u_1^*, u_2 = u_2^*, u_3 = u_3^*$. Thus, the solving u_1^*, u_2^*, and u_3^* gives

$$u_1^* = \frac{z_1}{E_1}, \qquad u_2^* = \frac{z_2}{E_2}, \qquad u_3^* = \frac{z_3}{E_3},$$

where

$$\begin{aligned}
z_1 &= (q_5 - q_7)\omega_1\tau_1 i_h + (q_6 - q_7)\omega_1\tau_2 i_a + (q_8 - q_{12})\omega_1\tau_{H1} i_{eh} + (q_9 - q_{12})\omega_1\tau_{H2} i_{lh}\\
&\quad + (q_{10} - q_{12})\omega_1\tau_{A1} i_{ea} + (q_{11} - q_{12})\omega_1\tau_{A2} i_{la},\\
z_2 &= (q_2 - q_4)\omega_2\sigma_1 i_e + (q_3 - q_4)\omega_2\sigma_2 i_l + (q_8 - q_5)\omega_2 i_{eh} + (q_9 - q_5)\omega_2 i_{lh} + (q_{10} - q_6)\omega_2 i_{ea}\\
&\quad + (q_{11} - q_6)\omega_2 i_{la},\\
z_3 &= \big((q_2 - q_1)s + (q_8 - q_5)\kappa_1 i_h + (q_{10} - q_6)\kappa_2 i_a\big)\omega_3\beta_S(i_e + \theta_1 i_{eh} + \theta_2 i_{ea})\\
&\quad + \big((q_5 - q_1)s + (q_8 - q_2)\nu_1 i_e + (q_9 - q_3)\nu_2 i_l\big)\omega_3\beta_H(i_h + \eta_1 i_a + \eta_2 i_{eh} + \eta_3 i_{ea} + \eta_4 i_{lh}\\
&\quad + \eta_5 i_{la}).
\end{aligned}$$

Since u^* must belong to Ω, the optimal control of u_1^*, u_2^*, and u_3^* will be obtained in equation (12). □

2. Numerical Simulation

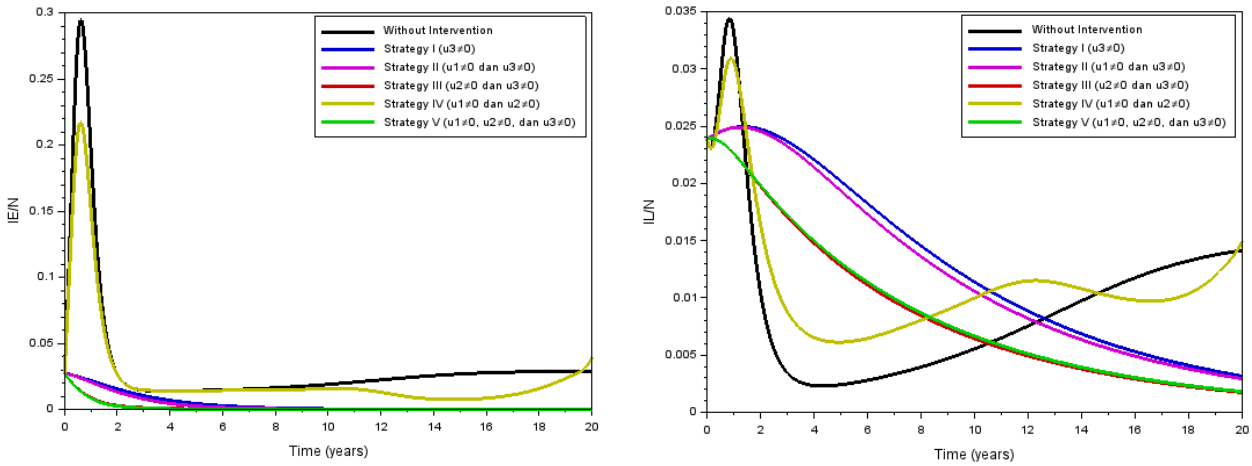
In this part, we show the effectiveness of control implementation in tackling the spread of syphilis and HIV/AIDS coinfection. Numerical simulations were carried out on five control strategies. The following control strategies are considered to assess the impact of prevention measures only (single control), combination of prevention measures with treatment, and combination of both treatments (multiple control) on the transmission dynamics of syphilis and HIV/AIDS coinfection.

In this simulation, the parameter values for numerical solving can be seen in Table 1, coefficients D_j, $j = 1, 2, 3, \dots, 8$, and relative cost E_i, $i = 1, 2, 3$ are assumed to be $D_j = 37$, $E_1 = 1$, $E_2 = 0.6$, and $E_3 = 0.15$. The assumption about the cost weight (E_i) is based on the fact that the cost of treatment is more expensive than the cost of prevention program (Chazuka et al., 2024). The initial value for each subpopulation in the form of proportion, namely $s(0) = 0.68259$, $i_e(0) = 0.02730$, $i_l(0) = 0.02389$, $r_s(0) = 0$, $i_h(0) = 0.05461$, $i_a(0) = 0.03413$,$p_h(0) = 0.01706$,$i_{eh}(0) = 0.04437$,$i_{lh}(0) = 0.01365$, $i_{ea}(0) = i_{la}(0) = 0.00683$, and $p_{sh}(0) = 0.08874$.

The optimal control set is determined by solving the optimality system, which includes the state system (2) and the costate system (10). These systems are numerically solved using the 4th order Runge-Kutta and Forward-Backward Sweep methods in Scilab-2024.0.0 (Lenhart & Workman, 2007). The dynamics of the infected subpopulation between control strategies over a 20-year time period are illustrated in the following Figure 2-4. The figure illustrates the impact of various intervention scenarios on the subpopulations of individuals with monoinfection and coinfection. The interpretation of the curves based on interventions is as follows: the black curve represents the condition without intervention, while the colored curves (blue, purple, red, yellow, and green) depict conditions with the corresponding interventions as outlined in Table 4.

Table 4. Control Strategies

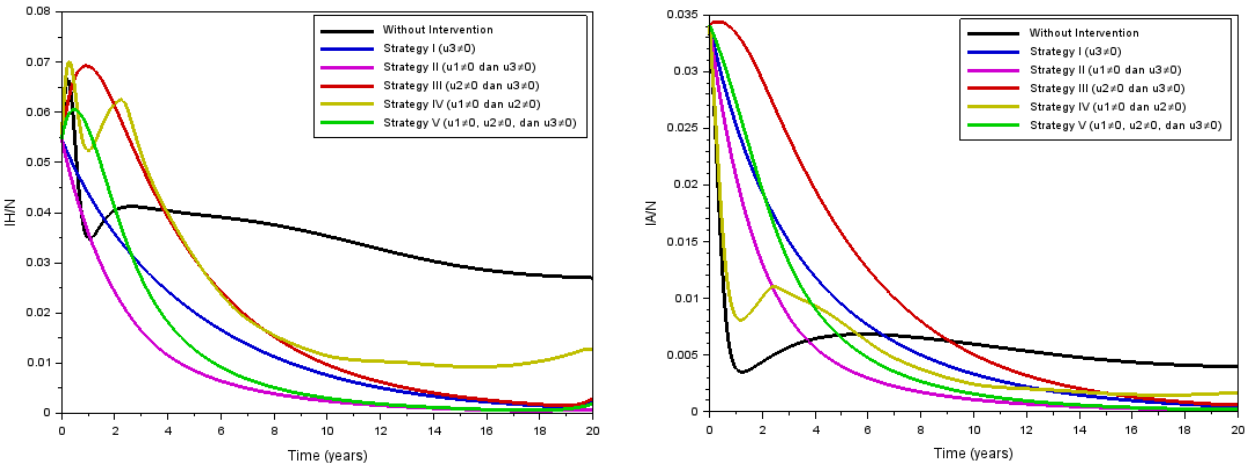
Strategy	Control			Description
	u_1	u_2	u_3	
I	-	-	on	Condom use only.
II	on	-	on	Treatment for HIV/AIDS and condom use at the same time.
III	-	on	on	Treatment for syphilis and condom use at any one time.
IV	on	on	-	Both treatments for syphilis and HIV/AIDS are carried out simultaneously.
V	on	on	on	All three controls are applied at the same time.



(a) (b)

Figure 2. Dynamics of individuals monoinfected with early-phase (a) and late-phase (b) syphilis to five different control strategies

Figure 2 demonstrates that the applied control strategies significantly reduce the proportion of individuals infected with syphilis compared to the no-intervention scenario. Specifically, strategy III (syphilis treatment and condom use) proves to be the most effective in reducing the proportion of individuals infected with syphilis, both in the early and late stages, achieving a 76.7% reduction in cases. This outcome is nearly equivalent to strategy IV, which results in a 76.5% reduction. However, in Figures 2a and 2b, strategy IV is less effective in reducing the curve of the syphilis-infected subpopulation, with a decrease of only 17.1%, which is significantly lower than strategy I and strategy II, which reduce cases by 60.5% and 63.4%, respectively. These findings show that a comprehensive approach that combines prevention and treatment is proven to be more effective in controlling infection (Dong et al., 2019; Momoh et al., 2021). Therefore, public health strategies should emphasize the importance of condom use as a primary measure while maintaining access to treatment to achieve optimal infection control.



(a) (b)

Figure 3. Dynamics of HIV-infected individuals (a) and advanced phases of AIDS (b) to five different control strategies

Figure 3 shows the dynamics of individuals infected with HIV and advanced stages of AIDS under five different intervention strategies. The black curve, which represents a scenario without intervention, shows that without control measures, the prevalence of HIV/AIDS remains high in the population. In the meantime, strategy III is not the best option to minimize the proportion of people infected with HIV/AIDS. This strategy actually causes an increase in the proportion of individuals infected with HIV/AIDS after the system implemented treatment for syphilis, as shown in Figure 3a-b. This increase is caused by syphilis treatment that is also given to individuals coinfected with syphilis and HIV/AIDS so that they recover from syphilis but remain infected with HIV. Of the five control strategies, strategy II is considered the best strategy to minimize the proportion of individuals infected with HIV/AIDS. This strategy combines preventive measures, such as condom use, with treatment for HIV/AIDS simultaneously, which can reduce the number of HIV/AIDS-infected individuals by up to 71.5%. This number is much higher than strategies I, III, IV, and V, which managed to reduce cases by 50.5%, 27.1%, 32.8%, and 58.7%, respectively. These results are consistent with research showing that a combination of antiretroviral therapy and prevention interventions can significantly reduce the spread of HIV (Chazuka et al., 2024; Tao et al., 2018). Thus, these findings confirm that an integrated approach combining treatment therapy and preventive measures with condom use has a greater impact than strategies implemented separately.

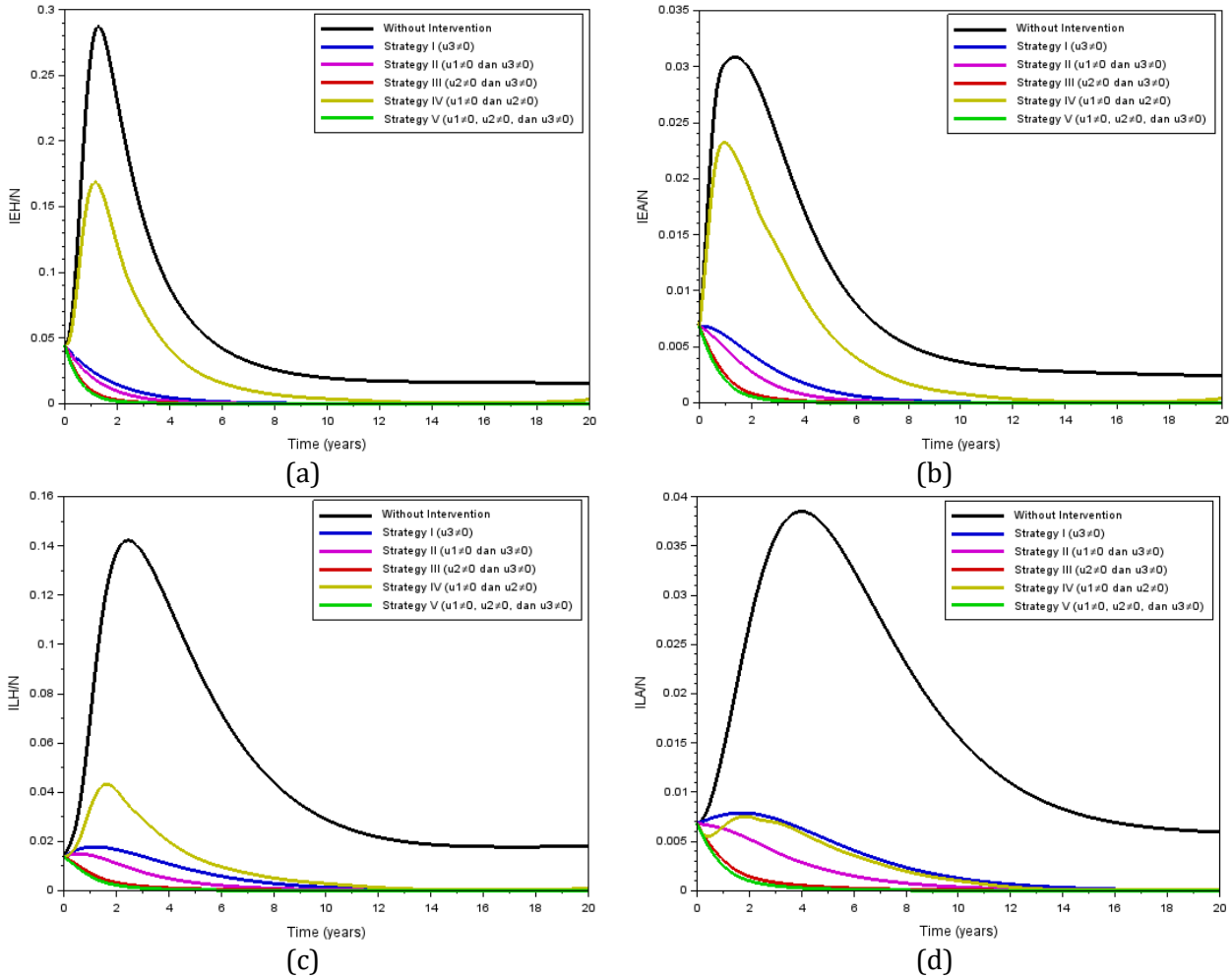
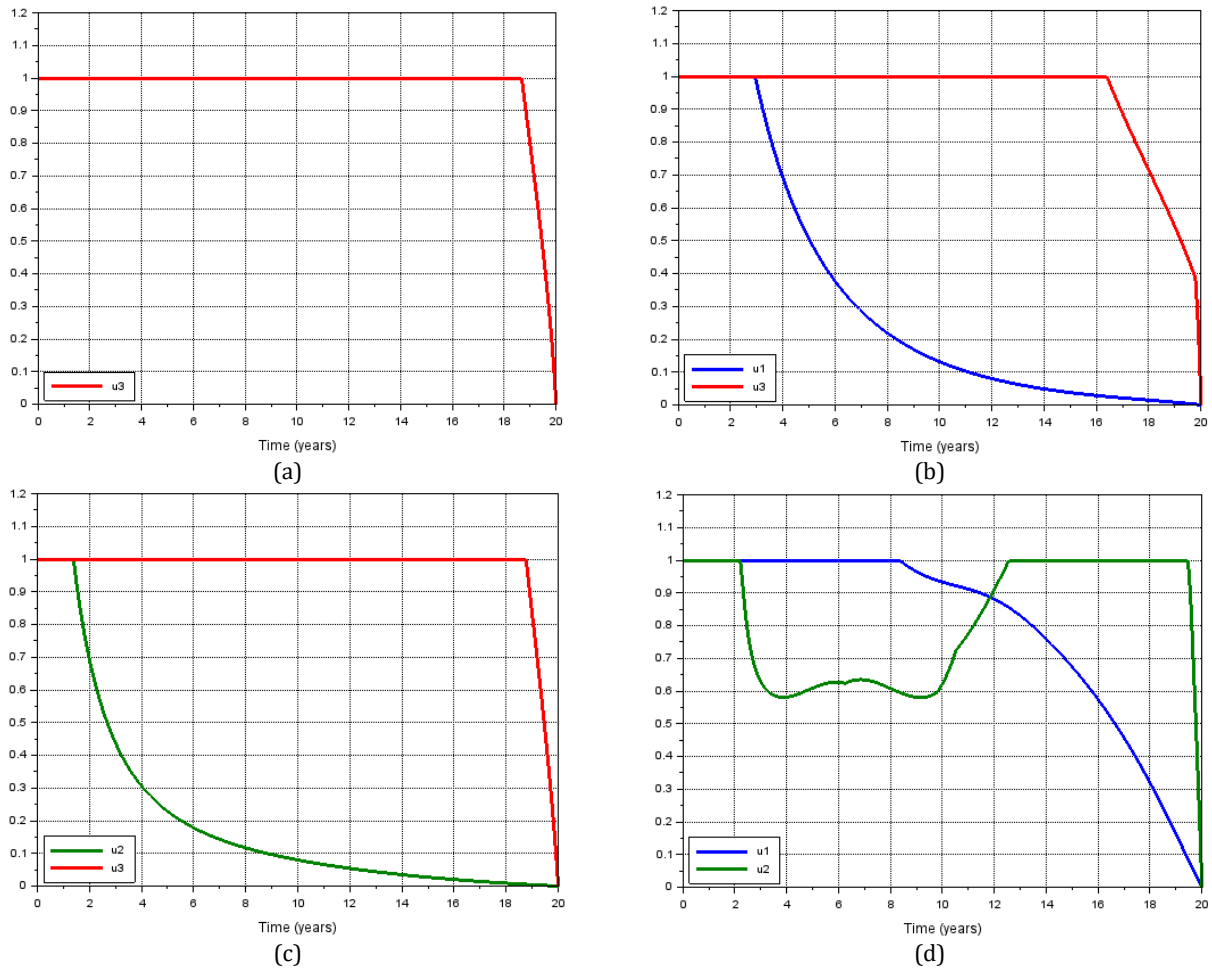
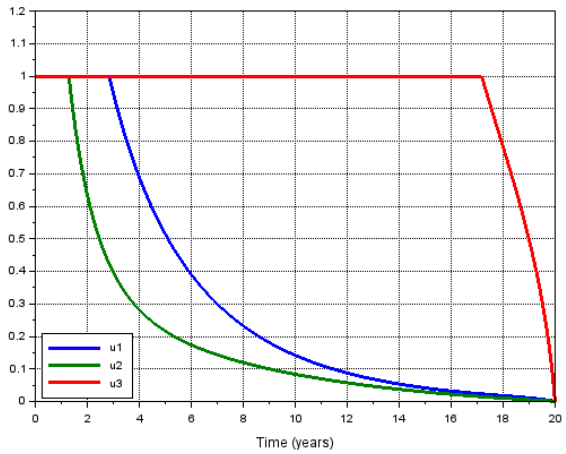


Figure 4. Dynamics of individuals coinfected with early syphilis-HIV (a), early syphilis-AIDS (b), late syphilis-HIV (c), and late syphilis-AIDS (d) to five different control strategies

Figure 4 depicts the dynamics of individuals with syphilis-HIV/AIDS co-infection in various stages of the disease under five different intervention strategies. In general, the five control strategies are equally effective in reducing infection rates and delaying the endemic peak in the subpopulation of coinfected individuals. However, based on the simulation results illustrated in Figure 4, strategy IV is considered the most effective strategy in reducing the number of syphilis and HIV/AIDS coinfected individuals. This control strategy is based on multiple controls that involve HIV/AIDS treatment, syphilis treatment, and condom use at the same time with an infection reduction rate of 97.8%. This result is almost equivalent to strategy III, which was able to reduce coinfection cases to 97.2%. On the other hand, strategy IV can only reduce the proportion of syphilis and HIV/AIDS coinfected individuals by 68.9%, while strategies I and II provide better results, reducing the coinfection rate by 90.5% and 94%, respectively. These results confirm that an integrated approach that combines syphilis and HIV/AIDS treatment with consistent and correct condom use is the most effective strategy in reducing the rate of transmission and reducing the number of individuals with coinfection. Figure 5 below depicts the changes in control variables over time to satisfy certain optimality criteria.





(e)

Figure 5. Control functions for strategy I (a), strategy II (b), strategy III (c), strategi IV (d), and strategy V (e)

To provide an optimal contribution, prevention effort in the form of using condoms appropriately and correctly are maximally applied at 100 percent capacity from the beginning until 19 year in strategy I. Furthermore, the control function for strategy II is shown in Figure 5b. The figure shows that condom use reaches a maximum level of 100 percent until around 16.6 year and can be reduced gradually. HIV/AIDS treatment effort is implemented at 100 percent capacity from the beginning until around 3 year. Then, it can be slowly reduced until the end of the period. For Figure 5c, when condom use control is applied together with syphilis treatment, condom use is provided at 100 percent level until around 19 year, while syphilis treatment should be enforced 100 percent from the beginning until around 1.7 year and slowly reduced until the end of the period in strategy III. However, when both HIV/AIDS and syphilis treatment effort is implemented together in strategy IV, HIV treatment should be implemented at the maximum level until 8.2 year and continuously reduced until the end of the period. Meanwhile, the syphilis treatment program should be carried out maximally until 2,2 year and at an interval of [12.7; 19.7]. Finally, if all controls are applied simultaneously, condom use control should be maximally applied at 100 percent capacity until around 17 year, while HIV/AIDS treatment should be applied at 100 percent from the beginning until around 3 year, and syphilis treatment is provided at a level of 100 percent in the interval [0, 1.7]. After that, it can be slowly reduced until the end of the period in strategy V.

3. Cost-Effectiveness Analysis

In selecting alternative strategies for health interventions that are most efficient and effective in reducing the economic burden and improving the quality of health services, this study applied the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) approaches (Agusto & Leite, 2019; Asamoah et al., 2022). ACER and ICER are calculated by the formula:

$$\text{ACER}\,(k) = \frac{\mathcal{C}_k}{\mathcal{M}_k}, \tag{15}$$

$$\text{ICER}\,(k) = \frac{\mathcal{C}_k - \mathcal{C}_{k-1}}{\mathcal{M}_k - \mathcal{M}_{k-1}}. \tag{16}$$

The results of the ACER and ICER calculations related to determining the optimal strategy in controlling syphilis and HIV/AIDS coinfection are described below. The total cost incurred to implement a particular intervention strategy is estimated from

$$\mathcal{C}_k = \int_0^{tf} \frac{1}{2}\left(E_1 u_{1,k}^2 + E_2 u_{2,k}^2 + E_3 u_{3,k}^2\right) dt,$$

while the health benefit (or number of infections prevented) during the control period is calculated as

$$\mathcal{M}_k = \mathcal{B}_0 - \mathcal{B}_k$$

with total infections after control measures for each intervention strategy $k = \text{I, II, III, IV, V}$

$$\mathcal{B}_k = \int_0^{tf} \left(i_{e,k} + i_{l,k} + i_{h,k} + i_{a,k} + i_{eh,k} + i_{lh,k} + i_{ea,k} + i_{la,k}\right) dt.$$

Total infections before control implementation

$$\mathcal{B}_0 = \int_0^{tf} (i_e + i_l + i_h + i_a + i_{eh} + i_{lh} + i_{ea} + i_{la})\, dt.$$

For each intervention strategy, the ACER and ICER calculations are organized in a Table 5 as follows:

Table 5. Numerical Results of Health Benefits, Total Costs, ACER, and ICER

Strategy	**Health Benefit** $(\mathcal{M}_k)$	**Total Cost** $(\mathcal{C}_k)$	**ACER**	**ICER**
0	0	0	NA	NA
IV	2.2107	11.3749	5.1455	D
I	3.2918	1.4391	0.4372	0.4372
III	3.4153	2.1769	0.6374	5.9738
II	3.5794	3.6108	1.0088	8.7353
V	3.6859	4.3201	1.1721	6.6630

Based on the identification results in Table 5, strategy IV is dominated by strategies I, II, III, and V because strategy IV has smaller benefits and higher costs. So, strategy IV should be excluded or ruled out (Ayele et al., 2021; ELmojtaba et al., 2024). As such, strategies I, II, III, and V are cost-effective strategies with strategy I being the cheapest or most efficient strategy as it has the smallest ACER and ICER values compared to the other strategies.

D. CONCLUSION AND SUGGESTION

A mathematical model including twelve different subpopulations was developed to describe the interaction between syphilis infection and HIV/AIDS. The model was used to evaluate the effectiveness of three interventions, namely HIV/AIDS treatment, syphilis treatment, and condom use as preventive measures. Among the tested strategies, strategy V proved to be the most effective in reducing the proportion of infected individuals. It achieved an 86.04% reduction in cases, surpassing strategies II, III, I, and IV, which reduced cases of 83.56%, 79.72%, 76.84%, and 51.61%, respectively. The superior performance of strategy V can be attributed to its comprehensive approach, which combines both treatment and prevention. While treatment alone helps manage infections in individuals already affected, it does not prevent new cases. By integrating condom use, strategy V directly reduces transmission, lowering infection rates more effectively than treatment-only strategies. This combined approach, which both treats existing infections and prevents new cases, establishes strategy V as the most effective control combination.

In addition to effectiveness, the cost-efficiency of each strategy was evaluated using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER). The results identified strategies I, II, III, and V as cost-effective, with Strategy I being the least expensive due to its lower ACER and ICER values. However, cost-effectiveness does not merely refer to the lowest-cost strategy but rather to the approach that provides the greatest health benefits per unit cost. While strategy I incurred the lowest costs, its effectiveness in reducing infections was lower than that of strategy V. Moreover, the ICER analysis revealed that strategy IV, which focuses solely on HIV/AIDS and syphilis treatment without incorporating condom use, is less effective than the other strategies that integrate prevention efforts. This further reinforces the importance of prevention in disease control. Since treatment alone does not stop the spread of infection, a strategy that includes preventive measures is crucial for long-term success in controlling syphilis and HIV/AIDS.

In conclusion, this study underscores that an integrated approach combining treatment and prevention yields the most effective results in controlling syphilis and HIV/AIDS coinfections. Strategy V, which incorporates both treatment and condom use, not only achieves the highest reduction in infections but also maximizes the impact of each intervention. These findings emphasize the need for public health policies that prioritize both treatment and preventive measures, as prevention, particularly through condom use, is the most effective way to reduce transmission and control the spread of syphilis and HIV/AIDS in the long term.

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